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MARSHALL O'TOOLE GERSTEIN MURRAY
AND BORUN
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO, IL 606066402

EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/419,545	DARJI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 anf 9-23* is/are pending in the application.

4a) Of the above claim(s) *11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 9, 10 and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 01/05/04 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 11/17/03 in response to the final Office Action mailed 08/13/03. With this, Applicants have amended the specification.

Status of Claims

3) Claims 7 and 8 have been canceled via the amendment filed 11/17/03.

Claims 1-6, 9 and 10 have been amended via the amendment 11/17/03.

New claims 17-23 have been added via the amendment 11/17/03.

Claims 1-6 and 9-23 are pending.

Claims 1-6, 9, 10 and 17-23 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the abstract made in paragraph 8 of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 4 of the Office Action mailed 08/13/03 is withdrawn in light of Applicants' amendment.

7) The objection to the specification made in paragraph 9(i) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 5 of the Office Action mailed 08/13/03 is withdrawn in light of Applicants' amendments to the specification.

8) The objection to the specification made in paragraph 9(v) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 6 of the Office Action mailed 08/13/03 is withdrawn in light of Applicants' amendments to the specification.

9) The objection to the specification made in paragraph 9(vi) of the Office Action mailed 03/29/02

(paper no. 17) and maintained in paragraph 7 of the Office Action mailed 08/13/03 is withdrawn in light of Applicants' amendments to the specification.

10) The objection to the specification made in paragraph 9(vii) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 8 of the Office Action mailed 08/13/03 is withdrawn.

11) The objection to claim 9 made in paragraph 14(d) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 10 of the Office Action mailed 08/13/03 is withdrawn in light of Applicants' amendments to the specification.

12) The objection to the specification made in paragraph 18 of the Office Action mailed 12/10/02 (paper no. 20) and maintained in paragraph 11 of the Office Action mailed 08/13/03 is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Moot

13) The rejection of claim 8 made in paragraph 13(c) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 25 of the Office Action mailed 12/10/02 (paper no. 20) and paragraph 14 of the Office Action mailed 08/13/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

14) The rejection of claims 7 and 8 made in paragraph 13(f) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 26 of the Office Action mailed 12/10/02 (paper no. 20) and paragraph 14 of the Office Action mailed 08/13/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

15) The rejection of claims 7 and 8 made in paragraph 11 of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 27 of the Office Action mailed 12/10/02 (paper no. 20) and paragraph 16 of the Office Action mailed 08/13/03 under 35 U.S.C § 112, first paragraph, with regard to the scope, is moot in light of Applicants' cancellation of the

claims.

16) The rejection of claims 7 and 8 made in paragraph 29 of the Office Action mailed 12/10/02 (paper no. 20) and maintained in paragraph 17 of the Office Action mailed 08/13/03 under 35 U.S.C § 102(e) as being anticipated by Curtiss III *et al.* (US 5,656,488), is moot in light of Applicants' cancellation of the claims.

17) The rejection of claims 7 and 8 made in paragraph 30 of the Office Action mailed 12/10/02 (paper no. 20) and maintained in paragraph 18 of the Office Action mailed 08/13/03 under 35 U.S.C § 102(b) as being anticipated by Srinivasan *et al.* (*Biol. Reproduct.* 53: 462-471, 1995), is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

18) The rejection of claim 1 made in paragraph 13(a) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 23 of the Office Action mailed 12/10/02 (paper no. 20) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

19) The rejection of claims 2-6 and 9 made in paragraph 13(f) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 26 of the Office Action mailed 12/10/02 (paper no. 20) and paragraph 14 of the Office Action mailed 08/13/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the base claim.

20) The rejection of claims 1-6, 9 and 10 made in paragraph 11 of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 27 of the Office Action mailed 12/10/02 (paper no. 20) and paragraph 16 of the Office Action mailed 08/13/03 under 35 U.S.C § 112, first paragraph, with regard to the scope, is withdrawn in light of Applicants' amendments to the base claim.

21) The rejection of claims 1-4 and 10 made in paragraph 29 of the Office Action mailed 12/10/02 (paper no. 20) under 35 U.S.C § 102(e) as being anticipated by Curtiss III *et al.* (US 5,656,488), is withdrawn in light of Applicants' amendment to the base claim.

22) The rejection of claims 1, 2 and 10 made in paragraph 30 of the Office Action mailed 12/10/02 (paper no. 20) and maintained in paragraph 17 of the Office Action mailed 08/13/03

under 35 U.S.C § 102(b) as being anticipated by Srinivasan *et al.* (*Biol. Reproduct.* 53: 462-471, 1995), is withdrawn in light of Applicants' amendment to the base claim.

23) The rejection of claims 1, 5, 6 and 9 made in paragraph 32 of the Office Action mailed 12/10/02 (paper no. 20) and maintained in paragraph 18 of the Office Action mailed 08/13/03 under 35 U.S.C § 103(a) as being unpatentable over Curtiss III *et al.* (US 5,656,488) in view of Rock (US 5,869,057), Vogelstein *et al.* (US 6,054,570) or Chada *et al.* (US 5,736,388), is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) Maintained

24) The rejection of claim 9 made in paragraph 13(c) of the Office Action mailed 03/29/02 (paper no. 17) and maintained in paragraph 24 of the Office Action mailed 12/10/02 (paper no. 20) and paragraph 14 of the Office Action mailed 08/13/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

Applicants contend that claim 9 depends from claim 1, which has been amended 'to recite the characteristics of the variant'.

Applicants' argument has been carefully considered, but is non-persuasive. Claim 1 recites the characteristics of a heterologous gene or gene fragment as the one encoding a polypeptide, a protein and/or an antigen, but does not recite the characteristics of the 'heterologous gene' which is a 'truncated variant'. It is unclear what part of the gene, or what length of the gene is truncated in the variant. How much of the original structure of the heterologous gene should be retained in a gene such that it qualifies as a 'truncated variant' is not clear. To obviate the rejection, it is suggested that Applicants delete the recitation 'variant of a' in lines 3 and 4 of claim 9.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

25) Claim 1 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 includes the limitation: gene or gene fragment encodes a polypeptide, a protein 'and/or' an antigen capable of ..... There is no descriptive support in the specification, as

originally filed, for the claimed attenuated *S. typhimurium* containing a gene or gene fragment that encodes a polypeptide, protein 'and' an antigen, as recited currently. Therefore, the above-identified limitation in the claims is considered to be new matter. *In re Rasmussen,* 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

26) Claim 18 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 18 includes the limitation: the antibody response comprises production of IgG1, IgG2 and'/or' IgA antibodies. However, there appears to be no descriptive support in the specification, as originally filed, for an attenuated *S. typhimurium* comprising an eukaryotic expression vector for the expression of a gene as recited that encodes a protein, polypeptide and/or an antigen which is capable of inducing a biased T-cell response as recited and an IgG1, IgG2 'or' IgA antibodies. Therefore, the above-identified limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

27) Claim 1 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 includes the limitation: gene fragment 'carried' by the vector within an open reading frame. Applicants point to claims 7 and 8 as well as page 4, line 20 and page 7, line 12 of the specification as providing support for the new limitation. However, line 20 of page is supportive of a *S. typhimurium* strain 'carrying' a plasmid encoding beta-galactosidase etc. Line 21 on page 2 of the specification describes a heterologous gene or gene fragment, or an autologous gene or a gene fragment 'comprised by the vector within an open reading frame' as was originally presented in claim 1. Line 10 of page 7 is supportive of '*Salmonellae* carrying eukaryotic expression plasmids'. Line 12 of page 7 of the specification does not appear to be relevant to the recitation 'carried by the vector'. The scope of the term 'plasmids' is different from the scope of the term 'vectors'. Therefore, the above-identified limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C § 112, Second Paragraph

28) Claims 1-6, 9, 10 and 17-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is indefinite in the limitation: 'a polypeptide, a protein', because it is unclear how a 'polypeptide' differs from a 'protein' in scope.

(b) Claim 1 is indefinite and confusing in the limitation: 'biased towards an inflammatory T-helper response', because it is unclear what is encompassed in this phrase. The metes and bounds of the phrase are indeterminate.

(c) Claims 9 and 23 are indefinite in the limitation: 'the heterologous gene is .... a non-hemolytic truncated variant' because it is unclear how a gene, as opposed to a gene product,

can be referred to as 'non-hemolytic'.

(d) Claim 10 lacks proper antecedent basis in the limitation: 'a *Salmonella* strain of claim 1'. For proper antecedence, it is suggested that Applicants replace the limitation with --the *Salmonella* strain of claim 1--.

(e) Claim 23 is vague and indefinite in the limitation 'truncated variant'. It is unclear what part of the gene, or what length of the gene is truncated in the variant. How much of the original structure of the heterologous gene should be retained in a gene such that it qualifies as a 'truncated variant' is not clear.

(f) Claims 2-7, 9, 10 and 17-23, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

29) Claims 1, 2, 10 and 18-20 are anticipated under 35 U.S.C. § 102(b) as being anticipated by Yang *et al.* (*J. Immunol.* 145: 2281-2285, 1990).

In the absence of a definition for the limitation in the instant specification: 'T-cell response is biased towards an inflammatory T-helper response', the phrase is interpreted in this rejection as an IL-2 and/or IFN-gamma-producing immune response. The limitation 'for a vaccination of vertebrates' represents the intended use of the claimed strain and has no patentable weight. The phrase 'eukaryotic expression vector' is interpreted as a vector that is capable of expression in a eukaryotic host.

Yang *et al.* taught an attenuated *S. typhimurium* LB5010 or SL3261 vaccine strain comprising the phage P22HT105 or the pKK-Imm63-67 plasmid. The vaccine strain expresses the heterologous *Leishmania major* gp63 surface protein antigen which is capable of inducing an antibody response and a proliferative, preferentially Th1 T-cell response to *Leishmania major* in mice on oral administration (see abstract; 'Materials and Methods' on page 2282; and second full paragraph in right column on page 2283). The antibody response is of IgG and the T cells are $CD4^{+}$, secreting IL-2 and IFN-gamma (see abstract; Table 1; second full paragraph in right column on page 2283; and Figures 3 and 4). Yang's attenuated *S. typhimurium* strain which elicited both an antibody response and a biased T-cell response in a murine vertebrate, as recited, is expected to be suitable for vaccination of vertebrates, absent evidence to the contrary. That

the vector in the prior art attenuated *S. typhimurium* strain was capable of expressing the heterologous eukaryotic gene in the vertebrate host is inherent from the teachings of Yang *et al.*

Claims 1, 2, 10 and 18-20 are anticipated by Yang *et al.*

30) Claims 1, 2 and 18-22 are rejected under 35 U.S.C § 102(b) as being anticipated by Tite *et al.* (*Immunology* 70: 540-546, 1990).

In the absence of a definition for the limitation in the instant specification: 'T-cell response is biased towards an inflammatory T-helper response', the phrase is interpreted in this rejection as an IL-2 and/or IFN-gamma-producing immune response. The limitation 'for a vaccination of vertebrates' represents intended use of the claimed strain and has no patentable weight. The phrase 'eukaryotic expression vector' is interpreted as a vector that is capable of expression in a eukaryotic host.

Tite *et al.* taught an attenuated *S. typhimurium* SL3261 comprising a plasmid encoding the heterologous influenza nucleoprotein gene from A.NT/60/68 virus which was able to induce both humoral and cell-mediated immune responses, particularly CD4+ virus-specific T cells and class II MHC-restricted cytotoxicity, but not virus-specific class I MHC-restricted cytotoxic T lymphocytes. Mice orally immunized with the nucleoprotein-expressing strain (i.e., the vaccine) mounted a strong anti-viral antibody response and an IFN-gamma and IL-2 response (see abstract). The attenuated *S. typhimurium* expressing the viral gene product induced both B cell or humoral (antibody) response and T cell or cell-mediated immune response to the nucleoprotein antigen and induced CD4+ virus-specific T cells capable of proliferation. Mice orally immunized with the nucleoprotein-expressing bacteria mounted a strong anti-viral antibody response, specific spleen cell proliferation and production of IFN-gamma and IL-2 (i.e., T-cell response biased towards an inflammatory T-helper or TH1 response). See abstract; Materials and Methods; Results; pages 542-545; and Table 1. Although Tite *et al.* are silent about the isotype composition of the serum antibody response elicited by their attenuated *S. typhimurium,* given the induction also of T-cell immunity, Tite's attenuated *S. typhimurium* is expected to induce one of IgG1, IgG2 or IgA antibodies. That the attenuation which occurred in the prior art *S. typhimurium* is suitable for vaccination of vertebrates, such as, humans, is inherent from the teachings of Tite *et al.* That the plasmid vector in the prior art attenuated *S.*

typhimurium strain was capable of expressing the heterologous eukaryotic gene in the vertebrate host is inherent from the teachings of Tite *et al.*

Claims 1, 2 and 18-22 are anticipated by Tite *et al.*

31) Claims 1, 9, 10, 17, 19, 22 and 23 are rejected under 35 U.S.C § 102(b) as being anticipated by Verma *et al.* (*Vaccine* 13: 142-150, 1996).

In the absence of a definition for the limitation in the instant specification: 'T-cell response is biased towards an inflammatory T-helper response', the phrase is interpreted in this rejection as an IL-2-producing immune response. The limitation 'for a vaccination of vertebrates' or humans represents intended use of the claimed strain and has no patentable weight. The phrase 'eukaryotic expression vector' is interpreted as a vector that is capable of expression in a eukaryotic host.

Verma *et al.* taught an attenuated *Salmonella* strain, *Salmonella dublin*, comprising a vector expressing class I MHC-restricted (CD8+) helper T-cell epitope of listeriolysin (LLO) of *L. monocytogenes* and class II MHC-restricted (CD4+) helper T-cell epitope of LLO which stimulated significant class-specific CTL and IL-2 responses (see abstract; Materials and Methods; Results; pages 148, 149; and Figures 4-6) and both class I and class II MHC-restricted immunity (see paragraph bridging left and right columns on page 143). A vaccine comprising the strain on a single immunization in mice expressed the heterologous antigens and conferred protection to mice when challenged with *L. monocytogenes* (see pages 144, 147 and 148; and Figure 7). That the vector in the prior art attenuated *Salmonella* strain was capable of express the heterologous eukaryotic gene in the vertebrate host is inherent from the teachings of Verma *et al.*

Claims 1, 9, 10, 17, 19, 22 and 23 are anticipated by Verma *et al.*

32) Claims 1-3, 10, 19 and 20 are rejected under 35 U.S.C § 102(b) as being anticipated by Fouts *et al.* (*Vaccine* 13: 1697-1705, 1995).

In the absence of a definition for the limitation in the instant specification: 'T-cell response is biased towards an inflammatory T-helper response', the phrase is interpreted in this rejection as an IFN-gamma-producing immune response. The limitation 'for a vaccination of vertebrates' or humans represents intended use of the claimed strain and has no patentable weight. The phrase 'eukaryotic expression vector' is interpreted as a vector that is capable of

expression in a eukaryotic host.

Fouts *et al.* taught the attenuated *aroA S. typhimurium* SL7207 vaccine strain comprising retroviral vectors expressing a heterologous HIV antigen, which elicited a heterologous antigen-specific Th1 response in mice with IFN-gamma production (i.e., a T-cell response biased towards an inflammatory T-helper response). The mice were immunized orally or intragastrically (see abstract; Figure 5; and pages 1698, 1700 and 1702). Fouts *et al.* taught that mice immunized orally with *S. typhimrium* SL7207 pYA::120 developed gp120-specific proliferative Th1 response and showed the production of IFN-gamma (see page 1703, right column).

Claims 1-3, 10, 19 and 20 are anticipated by Fouts *et al.*

Rejection(s) under 35 U.S.C. § 103

33) Claims 1, 4 and 5 are rejected under 35 U.S.C § 103(a) as being unpatentable over Tite *et al.* (*Immunology* 70: 540-546, 1990) or Verma *et al.* (*Vaccine* 13: 142-150, 1996) or Yang *et al.* (*J. Immunol.* 145: 2281-2285, 1990) or Fouts *et al.* (*Vaccine* 13: 1697-1705, 1995) in view of Rock (US 5,869,057, already of record) or Sztein *et al.* (*J. Immunol.* 155: 3987-3993, 1995).

Claim 1 is included in this rejection since claim 4 includes the limitation, 'claim 1'.

The reference of Rock, are applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a).

The teachings of Tite *et al.*, Verma *et al.*, Fouts *et al.*, or Yang *et al.* are explained above, which do not disclose their *Salmonella* strain to be *S. typhi* or *S. typhi* Ty21a.

However, the specific and conventional use of Ty21a strain of *Salmonella typhi* to express foreign proteins was well known in the art at the time of the instant invention. For example, Sztein *et al.* taught that attenuated *S. typhi* vaccine strain CVD 908 serves as a live vaccine vector and elicits CD8+ class I MHC-restricted CTL response. Sztein *et al.* expressly recommended or encouraged the use of this strain for future use as a live vector vaccine to stimulate specific CTL response against relevant foreign antigens (see abstract). Similarly, Rock taught the use of an attenuated strain of *Salmonella typhi,* Ty21a for carrying a heterologous eukaryotic gene specifying a foreign antigen (see section 2.3.6 Salmonella). The expression operon that is inserted is the beta-galactosidase gene (see second full paragraph in column 21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Rock's attenuated strain of *Salmonella typhi* Ty21a, or Sztein's CD8+ CTL-inducing attenuated *S. typhi* vaccine strain CVD 908 in place of Tite's, Yang's or Fouts' *S. typhimurium* strain, or Verma's *S. dublin* strain to produce the attenuated *S. typhi* strain of claim 4, or the attenuated *S. typhi* Ty21a strain of claim 5, with a reasonable expectation of success, since Rock showed that it was conventional to use *Salmonella typhi,* Ty21a to express a foreign gene, and since Sztein *et al.* expressly recommended or encouraged the use of the attenuated *S. typhi* vaccine strain for future use as a live vector vaccine to stimulate specific CTL response against relevant foreign antigens.

Claims 1, 4 and 5 are *prima facie* obvious over the prior art of record.

34) Claim 6 is rejected under 35 U.S.C § 103(a) as being unpatentable over Tite *et al.* (*Immunology* 70: 540-546, 1990) or Verma *et al.* (*Vaccine* 13: 142-150, 1996) or Yang *et al.* (*J. Immunol.* 145: 2281-2285, 1990) or Fouts *et al.* (*Vaccine* 13: 1697-1705, 1995) as modified by Rock (US 5,869,057, already of record) or Sztein *et al.* (*J. Immunol.* 155: 3987-3993, 1995) as applied to claim 1 above, and further in view of Vogelstein *et al.* (US 6,054,570, already of record), Chada *et al.* (US 5,736,388, already of record), or Frankel *et al.* (US 6,099,848, filed 11/18/1997).

The references of Rock, Vogelstein *et al.*, Chada *et al.* and Frankel *et al.* are applied in this rejection because they qualify as prior art under subsection (e) of 35 U.S.C § 102 and accordingly are not disqualified under U.S.C 103(a).

The teachings of Tite *et al.*, Verma *et al.*, Fouts *et al.*, or Yang *et al.* as modified by Rock or Sztein *et al* are explained above, which do not disclose their *Salmonella* strain as comprising the pCMV-beta gal expression vector as recited in claim 6.

However, the inclusion of the pCMV-beta-gal expression vector in a recombinant strain was well known in the art at the time of the instant invention. For example, Vogelstein *et al.* or Chada *et al.* taught the conventional use of the commercially available plasmid expression vector pCMV-beta-gal. See the paragraph bridging columns 5 and 6 of Vogelstein *et al.* and the first full paragraph in column 36 of Chada *et al.* Similarly, Frankel *et al.* disclosed that a heterologous antigen can be expressed in a bacterial vaccine vector under the control of

eukaryotic promoter/regulatory sequences. An exemplified vector is pCMVbeta comprising the immediate early promoter/enhancer region of human cytomegalovirus and those which include the SV40 early promoter region or the mouse mammary tumor virus LTR promoter region (see second full paragraph in column 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate Chada's, Vogelstein's or Frankel's pCMV-beta-gal in Tite's, Yang's, Verma's or Fouts' attenuated *Salmonella* strain as modified by Sztein *et al.* or Rock to produce the instant invention, with a reasonable expectation of success, since Frankel *et al.* taught that recombinant incorporation of pCMV-beta-gal was conventional during the expression of a protein in a bacterial vaccine vector. The incorporation of an art-known expression vector into an art-known attenuated *Salmonella* strain would have been well within the realm of routine experimentation, would have been obvious to one of skill in the art, and would have brought about similar effects, absent evidence to the contrary.

Claim 6 is *prima facie* obvious over the prior art of record.

Remarks

35) Claims 1-6, 9, 10 and 17-23 stand rejected.

36) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

37) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

38) Any inquiry concerning this communication or earlier communications from the

Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER